Abstract

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Synthesis of fluorescent polyene ceramides
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Ceramides are lipid compounds that belong to the sphingolipid family. These molecules play a crucial role in many biological processes e.g. they are secondary messengers during apoptosis and other cellular signaling pathways, are involved in the synthesis of sphingomyelin and play very important role in the lipid matrix of stratum corneum, which is the epidermal barrier.

Recent results showed that ceramides are affecting, or are being affected by various skin diseases. In the case of atopic dermatitis, a major decrease of ceramides in the stratum corneum is observed. On the other hand, the manifestation of psoriasis or atopic dermatitis can be reduced with topically administered ceramides. The topical ceramides repair the skin lipid barrier and prevent further water loss and aggravation of the disease.

The mechanism of action of topically administered ceramides has not been fully elucidated yet. This is one of the reasons why the selection of the right methodology in order to clarify the mechanism of action is crucial.

One of the possibilities is the introduction of a fluorophore into the ceramide molecule. Currently, various fluorophores (NBD, Bodipy, Rhodamine) are used but because of their bulkiness they can undesirably affect the physicochemical properties of such lipids and, consequently, their transport and metabolism.

As the most convenient fluorophores, molecules with conjugated *trans*-double bond system are used. This moiety mimics the structural and physicochemical properties of naturally occurring ceramides; thus the imaging methods based on these substances are more accurate.

The aim of this work is to explore synthetic routes towards polyene-fluorophore-bearing ceramide, in particular containing 5 *trans*-double bonds. For the synthesis of the key intermediate with terminal halogen in the sphingosine chain, were tried three synthetic pathways. Two of them were based on vinylation and alkylation of Garner aldehyde, and unfortunately failed because of low yields and difficult isolation of 5C sphingosine analog in the first case and because of the difficulty in the reduction of the triple bond in the the second approach. The third approach successfully used the Grubbs metathesis on a commercially available ceramide.

The polyene fluorophore (2*E*,4*E*,6*E*,8*E*)-deca-2,4,6,8-tetraenal was meant to be attached to the sphingosine residue by Wittig reaction. This aldehyde was synthesized in a multistep synthesis which is described as the fourth synthetic pathway of this work.

All the synthetic routes will be used in the future for the synthesis of the key compound - polyene fluorophore-bearing ceramide.